## REMARKS

Claims 1-4, 6, and 8-15 are pending; claims 5 and 7 having been cancelled; and claim 15 having been withdrawn in view of restriction.

New claim 16, fully supported by the originally-filed specification, has been added.

Applicants thank the Examiner for withdrawing the rejection of claims 3 and 10-14 under 35 U.S.C. § 112, second paragraph, as being indefinite in view of Applicants' claim amendments.

Applicants acknowledge the Examiner's rejection of claims 1-4, 6, and 8-14, under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient enablement. Applicants have provided rebuttal arguments and claim amendments to obviate this rejection.

Applicants acknowledge the Examiner's rejection of claims 1-4, 6, 10-11, and 14 under 35 U.S.C. § 102(b), as allegedly being anticipated by Goessl et al. (Cancer Research, 2000, Vol. 60, page 5941). Applicants traverse this rejection.

No new matter has been added.

### *Rejections under 35 U.S.C. § 112, second paragraph*

The Examiner rejected claims 1-4, 6, and 8-14 under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient enablement. Applicants have provided rebuttal arguments and claim amendments to obviate this rejection.

Specifically, discussing the *WANDS* factors (1-8, already of record) and reciting the various elements of Applicants' claims, the Examiner states that "while the art does enable one of skill in the art to analyze cytosine methylation in free floating DNA neither the art nor the specification enables one of skill in the art to determine the presence or absence of ANY cellular proliferative disease in a tissue, cell type or organ."

*Breadth of claims*. The Examiner reiterates Applicants' claim elements.

*Nature of the Invention.* The Examiner states that the claims broadly encompass ANY diseased condition that originates from ANY tissue, cell type, or organ. The Examiner further states that "the invention is in a class of invention which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology' (citing Mycogen Plant Sci., Inc. v. Monsanto Co)."

*Teachings of specification and state of the art.* The Examiner states that "the specification asserts a means to predict which organ, tissue, or cell type has developed a medical condition, by employing means of distinguishing between DNA originating from different tissues, organs, or cell types of the human body (citing page 19 last paragraph)" and that "characteristic methylation patterns of certain genes can be positively correlated with specific organs, tissues, cell types," but that "the specification does not disclose an association in any individual such as a dog, cat or peacock only human," and further "does not provide a predictive association of the detection of any disease by the detection of methylation patterns," that it "is unpredictable that any disease would be detectable in free floating DNA because it is unclear if any tumor, organ, or tissue can be detect[ed] in a fluid sample," and that it would therefore require undue experimentation to practice the invention as claimed, and that the specification teaches that "validation experiments are sometimes needed." The Examiner concludes (citing post-filing art; *Cottrell*) that, based on the specification and teachings in the art, it is unpredictable to correlate the methylation pattern of any free floating DNA to ANY disease or condition by detecting methylation patterns (or merely DNA) because the art teaches "lack of predictability with regard to methylation pattern studies and correlation to any disease condition." The Examiner urges that methylation patterns are not reproducible (citing Ziegler). Finally, the Examiner states that the specification teaches that the correlation of disease and free-floating DNA "must have an association step to compare to a normal individual and a validation step."

*The predictability or unpredictability of the art and degree of experimentation.* The Examiner states that genetic variations and associations are often irreproducible (citing Hirschhorn), unpredictability in associating circulating DNA with disease (citing Bremnes, Jung, and Sidransky). The Examiner states (citing Yates) that methylation is not only caused by neoplasms, but that methylation can be detected in normal tissue (e.g., from aged individuals), and that detection of methylation does not, therefore, necessarily indicate neoplastic tissue.

*Amount of direction or guidance provided by the specification.* The Examiner states that the specification does not provide specific guidance as to how to correlate detection of ANY disease by the detection of free floating DNA and that correlation must include and association step to compare methylation patterns to normal individuals and a validation study to confirm detection. The Examiner states that the art teaches confirmation in multiple large sampling sizes.

*Working Examples.* The Examiner states that the specification provides no examples to correlate detection of disease by detection of free floating DNA in any individual, because no "pvalue" is provided (citing Example 1 and Figure 7), or statistical significant association, and that the specification does not have an example of determining in ANY sample a correlation of methylation pattern with detection of ANY diseased condition. Finally, the Examiner states that the art teaches that the correlation of methylation patters to any disease in any population is not reproducible.

*Quantity of Experimentation.* The Examiner states that the quantity of experimentation needed is extremely large, because the artisan would need to the association of detection of disease with measurement of free floating DNA, determine if the association was species based, and that this would require significant effort to practice the invention as presently claimed.

*Level of skill in the art.* The Examiner states that the level of skill in the art is deemed to be high.

*Conclusion by Examiner*. The Examiner concludes that despite the level of skill in the art being high, given the specification guidance and working example, it would require *undue* experimentation to practice the invention as claimed.

Applicants respectfully traverse the Examiner's enablement rejection in view of Applicants' present claim amendments and in view of the applicable law.

**Applicants' maintained traversal**:

Applicants respectfully traverse the Examiner's rejection with respect to the presently amended claims, because the Examiner has not established a *prima facie* case of lack of enablement, as the proper inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require *undue* experimentation to make and use the subject matter as claimed, and, as discussed below in detail, such is not the case.

**Relevant Law**:

Applicants maintain that to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without *undue* experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir., 1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 471 F.2d 1237, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. In re

Anderson, at 1241 (citing Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935)). Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). There is, therefore, no requirement for disclosure of every species within a genus. Applicants are entitled to claims that are commensurate in scope not only with what Applicants have specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicants have disclosed.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of lack of enablement, as the proper inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require ***undue*** experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is **routine experimentation**. As appreciated by the Examiner, the amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

**Analysis**

***Claim scope and amendments***. In response to the Examiner's comments, Applicants have herein amended claim 1 to recite:

"A method for detecting the presence of a disease characterized by an increased amount of organ-specific free floating DNA ~~cellular proliferative disease in a tissue, cell type or organ of a human~~, comprising:

obtaining a bodily fluid sample from a test human;

determining an amount or presence of free floating DNA that originates from a particular ~~tissue, cell type or~~ organ in the sample comprising analysing for a DNA methylation pattern that is characteristic for the particular ~~tissue, cell type or~~ organ; and

determining the presence of a disease characterized by an increased amount of organ-specific free floating DNA ~~cell proliferative disease~~ based on comparing the amount or presence of free floating DNA that originates from the particular ~~tissue, cell type or~~ organ of the test human, with that of a normal control value."

Conforming amendments have also been made to claims 2, 6, 10, 11, 12, and 13.

The claim amendments serve to clarify the claimed subject matter by: (i) limiting the diseases to those characterized by an increased amount of organ-specific free floating DNA, as supported by the specification; (ii) limiting the individuals to humans, as supported by the specification; (iii) limiting the methylation pattern specificity to that of organ-specific methylation patterns; and (iv) providing, as suggested by the Examiner, an association step to compare results with normal individuals.

Support for the amendments is found in the originally filed specification. For example, support for "increased amount" is found at page 1, first paragraph, page 8, last paragraph, etc. Support for comparing is found, for example, in the following specification paragraphs:

"[0168] In the third step of the method, it is concluded whether a medical condition such as cell proliferative or inflammatory disease at the specified source is causing the release of DNA into the bodily fluid. *The presence or absence of a medical condition in said organ is determined*

*by comparing the individual's test result with the dataset that was built up in house in previous studies.*

[0174] Wherein said optional step has been performed, it is also preferred that in another additional fourth step, the presence or absence of a medical condition in said organ is determined *by comparing the individual's test result, regarding the fraction of free floating DNA that originates from a specific source with the dataset that was built up in house in previous studies.* Said fraction is determined by building the ratio of the amount of free floating DNA that can be correlated to a specific cell type, tissue or organ as source, and the amount of total free floating DNA. Based on these results it is possible to identify patients with abnormal amounts of DNA of a certain organ or tissue, as in increased by more than 10% *above a value defined as 'normal,'* in their bodily fluids. In a preferred embodiment it is possible to positively identify patients with free floating DNA levels increased by at least but not limited to 20% *above a value defined as normal.* In a further preferred embodiment it is possible to identify patients with an increased level of free floating DNA, specified in increased by at least but not limited to 40% above normal.

[0236] The amplification of said fragment indicated the presence of a specific methylation pattern in said informative CpG positions (of EYA 4). *From comparing the test result and the intensity of the fluorescent signal with a data set obtained from other samples* it could be concluded that a significant part of the DNA in the patients sample originated from colon. This result allowed the physician to refer said patient to an expert in gastrointestinal diseases."

No new matter has been added.

***Teachings of specification and state of the art.*** Regarding the Examiner's above-summarized comments with respect to specification teachings and the state of the art, and regarding any alleged requirement for validation, Applicants contend that the present teachings

have been misconstrued by the Examiner, and respectfully point out that the specification in fact teaches that the detection of an organ-specific methylation pattern in the free-floating DNA is indicative a disease of said organ, and that while this result invites the practitioner to now adventitiously *focus* on said organ (*e.g.*, when further analyzing the patient's potential disease, or treatments, etc.), whether or not the practitioner employs another *adjunct* method to further confirm or further validate a final diagnosis is discretionary, and there is no teaching in the specification, including the text cited by the Examiner about a *necessity* to perform further analyses to practice the invention as currently claimed. Specifically, the specification states that "[t]he next step *could* be to employ ..." (emphasis added). Therefore, it is inappropriate to construe the specification as teaching that validation studies are sometimes needed to associate detection of free floating DNA with detection disease. Obviously, there are options to further characterize the disease (e.g., with respect to grade, or specific sub-types of disease), as in any other diagnostic method. However, as taught by Applicants, a correlation can be made, for example, between a substantial amount of free floating DNA originating from liver, and the fact that the patient bears a diseased liver, without such further characterization options.

With respect to the Examiner's comments regarding inclusion of an association step to compare results with normal individuals, Applicants point out that the specification teaches either comparing the achieved measurements (e.g., methylation amount)s in a test patient's sample either with measurements with other diseased patient's or with samples from humans clearly diagnosed healthy (i.e. with controls). Applicants, however, additionally point out that the specification does not indicate that a comparison study must be done each time, when detecting methylation in a test sample (e.g., where control values of healthy individuals have been determined and are known, such that the comparison is with a data base or threshold value, etc.). Applicants have, nonetheless, amended the claims as described above to include such a comparison.

With respect to the Examiner's comments on the post-filing art of Cotrell et al., Applicants agree that methylation-based studies must have adequate requirements for consistency and performance, and defined clinical questions, sample sets, and methodologies coupled with current methylation technology. Indeed, Applicants contend that the teachings of the instant specification in combination with the skill in the art provide these benchmark requirements. Moreover, Applicants have amended the claims as described above to limit the claims to detection of diseases of particular organs and that are accompanied by an increased level of the particular organ-specific DNA in the blood or body fluid.

With respect to the Examiner's comments relating Applicants' Figure 7, the Examiner initially urges the "unpredictability" of the analyte (i.e. circulating DNA, as it was postulated in a single prior art document; Ziegler), and then alleges the "unpredictability" of the technology (methylation pattern analysis) *per se*. The examiner quotes Ziegler for the proposition that the fraction of plasma DNA contributed by tumors varies.

*First*, it is irrelevant to the presently claimed method whether the amount of tumor DNA circulating in the plasma (i.e. the "fraction of plasma DNA contributed by tumors") is highly variable (3 - 93%), because, with respect to diagnostic utility, it is not the fraction of DNA that is contributed *by the tumor* which is measured in the body fluid as claimed, but the fraction of DNA that is contributed *by the affected organ*, that is material There is no assertion in Ziegler that this fraction would be unpredictably variable.

*Second*, it is irrelevant to the presently claimed method whether Ziegler asserts that the levels of correlation between levels of total circulating DNA and cancer are variable. The correlation between circulating DNA level and cancer has been discussed in detail in the specification at pages 8 and 9, where the specification teaches that "elevated levels of circulating DNA appear to be characteristic for most but not all of the carcinoma diseases." The source of the

whole amount of free floating (i.e. circulating DNA) in blood may be caused by a variety of reasons, such as treatment of the cancer patient with a rather toxic agent (e.g., a chemotherapeutic agent). For example, evidence is discussed in Jahr et al. (*Cancer Res* 61 (2001):1659-1655) that circulating DNA might originate from apoptotic and necrotic cells, whereas Anker et al. (*Cancer Metastasis Rev.* 18 (1999): 65-73) discusses that the origin likely involves "active release," rather than lysis of circulating cancer cells from necrosis or apotosis. The studies Ziegler analyzed, therefore, might simply not have been suited to study the direct correlation. In any event, it is irrelevant to the method as claimed whether the entire amount of circulating DNA correlates to cancer or not, because it is the amount of *organ-specific* circulating DNA, which is the analyte of interest, and which is correlated to the presence of a diseased organ.

*Third*, The Examiner urges that Ziegler asserts that methylation studies were not always reproducible, because contradictory results have been published. There are, however, many art recognized examples (e.g., APC for lung cancer) demonstrating the reliability of detecting methylation patterns using suitable markers and the fact that the Examiner has construed Ziegler to the contrary does not support a general conclusion that methylation pattern analysis is unpredictable *per se*.

*Fourth*. Applicants have limited the claimed subject matter by: (i) limiting the diseases to those characterized by an increased amount of organ-specific free floating DNA, as supported by the specification; (ii) limiting the individuals to humans, as supported by the specification; (iii) limiting the methylation pattern specificity to that of organ-specific methylation patterns; and (iv) providing, as suggested by the Examiner, an association step to compare results with normal individuals.

***The predictability or unpredictability of the art and degree of experimentation.***

Regarding the Examiner's statements with respect to predictability or unpredictability of the art (in view of Hirschhorn, Bremnes, Jung, and Sidransky) and degree of experimentation, as discussed herein above, while there may be unpredictable variation in the total amounts of free-floating DNA, such variation is irrelevant for the method as claimed, as Applicants' claimed inventive methods comprise a correlation between organ-specific circulating DNA and disease of said organ. That is, while the clinical value of a total amount of circulating DNA may be questionable or unpredictable, the analysis of organ specific fractions therein is highly informative as disclosed and claimed by the present Applicants.

With respect to the Examiner's comments regarding the teaching of Yates that methylation can be detected in normal tissue, Applicants respectfully point out that it is well appreciated in the art that methylation patterns may not only be indicative of cancer (neoplasm), but also bear additional information (e.g., aging, development, etc). Applicants' claimed methods, however, use the methylation status of CpG dinucleotide sequences as diagnostic tools where they are methylated in a pattern specific to a particular organ (e.g., regardless of the age status of said organ, see, e.g., page 35, second paragraph.

> "[0133] If a CpG positions is only ever specifically methylated when the corresponding DNA sequence was isolated from one cell type, for example, kidney cells but said CpG position is not methylated when the DNA was isolated from another cell type, for example, liver cells, blood cells, bladder cells or colon cells etc. said CpG position is an 'informative CpG position.' A DNA sequence carrying one or more informative CpG positions in this context is called a 'marker gene', regardless whether it is a gene in the common sense or not."
>
> also in [0170]:
>
> "Those genes contain informative CpG positions, CpG positions that are differentially methylated, specifically for the tissue the DNA has been isolated from."

***Amount of direction or guidance provided by the specification.*** Regarding the

Examiner's statements with respect to the amount of direction or guidance provided by the specification, Applicants point out that it is misleading for the Examiner to judge sufficiency of guidance by stating that "the specification does not provide any guidance as how to correlate detection of disease by the detection of free floating DNA," in view of the fact that the specification in fact teaches that an *increased* level of organ-specific circulating DNA is indicative of said diseased organ.

Likewise, the specification has been mischaracterized by the Examiner, because the specification does not, as alleged by the Examiner, teach that a correlation *must* include an active association step to compare methylation patterns to individuals, but simply teaches to compare methylation patterns or methylation analysis results with results from other appropriate samples, when the result is to be used to conclude upon presence or absence of a medical condition in said organ.

> "[0168] In the third step of the method, it is concluded whether a medical condition such as cell proliferative or inflammatory disease at the specified source is causing the release of DNA into the bodily fluid. The presence or absence of a medical condition in said organ is determined by comparing the individual's test result with the dataset that was built up in house in previous studies. which may originate from healthy donors or other unambiguously diagnosed patient samples.

As described above, the claims have been amended to include the recitation, "...based on comparing the amount or presence of free floating DNA that originates from the particular organ of the test human, with that of a normal control value."

Moreover, as discussed above in detail, the specification also does not indicate that a correlation *must* include a *validation study* to confirm detection of disease. Rather, the specification teaches that it is an option for the practitioner to further analyze the organ identified as the source of DNA, or alternatively use the DNA sample for further analysis, as for example, by

applying a cancer stage-specific markers.

> "[0168] ... Wherein the extracellular DNA can clearly be correlated to a specific organ or tissue as the predominant source a further analysis of said organ or tissue--or a further analysis of said DNA by means of cancer marker genes--as described elsewhere--is highly indicated."

***In summary***, Applicants point out that with respect to enablement, ALL of the Wands factors must be considered by the Examiner and not merely the *predictability* factor. Additionally, under U.S. Patent Law, a considerable amount of experimentation is permissible, particularly if it is routine experimentation. As appreciated by the Examiner, the amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Applicants submit that given the teachings of the specification, the steps of obtaining a bodily fluid sample from a test human; determining an amount or presence of free floating DNA that originates from a particular organ in the sample comprising analysing for a DNA methylation pattern that is characteristic for the particular organ; and determining the presence of a disease characterized by an increased amount of organ-specific free floating DNA based on comparing the amount or presence of free floating DNA that originates from the particular organ of the test human, with that of a normal control value, does not amount to undue experimentation. If any experimentation is required to practice the present claims, such experimentation is merely routine and not undue upon consideration of all of the *Wands* factors. The Examiner has offered insufficient evidence to support that any such required experimentation is other than routine. As

appreciated by the Examiner, the level of skill in the art at the time of filing was and is high, and given the instant teachings and those of the art, determination of the methylation state of one or more CpG residues in free floating DNA, relative to a control, could be done by one of ordinary skill in the art at the time of filing in a matter of a few days or a week using routine, standard DNA manipulation methods and methylation assays available at the time of filing of the present application.

Applicants point out that the claims have already been limited the claimed subject matter by: (i) limiting the diseases to those characterized by an increased amount of organ-specific free floating DNA (e.g., cancers characterized by an increased amount of organ-specific free-floating DNA), as supported by the specification; (ii) limiting the individuals to humans, as supported by the specification; (iii) limiting the methylation pattern specificity to that of organ-specific methylation patterns; and (iv) providing, as suggested by the Examiner, an association step to compare results with normal individuals. In light of the scope of the claims, the teachings in the specification, the presence of specific examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art (as exemplified by the Examiner's own cited literature), and the predictability of the subject matter, Applicants respectfully submit that one of skill in the art could readily make and use the presently claimed subject matter without undue experimentation.

Applicants point out that the Examiner has provided no reason as to why Applicants' claim 12, which does not have a "disease characterized by an increased amount of organ-specific free floating DNA" limitation, is not allowable, and Applicants respectfully contend that claim 12 is allowable along with the other claims.

Detection of disease with methylation patterns in free floating DNA is *not* unpredictable, as was discussed in Applicants' last Response and Amendment, where the method has been

confirmed by the use of the colon cancer marker Septin 9, for methylation, which has repeatedly and predictably been correlated to colon cancer, and which is currently developed to become an approved blood based colon cancer marker.

Accordingly, for all of the aforementioned reasons, Applicants respectfully submit that the basis for this rejection has been overcome, and request that the rejection be withdrawn.

***Rejections under 35 U.S.C. § 102***

The Examiner rejected claims 1-8, 10-11, and 14 under 35 U.S.C. § 102(b), as allegedly being anticipated by Goessl et al. (Cancer Research 2000 Vol. 60, page 5941).

Applicants presume that Examiner is rejecting claims 1-4, 6, 8, and 14, because claims 5 and 7 have been previously cancelled, and the Examiner states at page 28 of the Action that the 102 rejection was withdrawn with respect to claims 10-13.

Specifically, the Examiner urges that Goessl teaches determining prostate cancer based on the presence of GSTP1 in bodily fluids.

Applicants traverse this rejection, based on the present amendments to the claims, which now recite "organ-specific free floating DNA."

Applicants respectfully point out that the present invention is based on the use of organ markers or tissue markers, which are nucleic acids bearing organ or tissue specific methylation patterns, independent from the question whether the organ or tissue is diseased or not. Whereas, the prior art merely teaches the use of cancer markers, such as for example GSTP1, which is a nucleic acid bearing a cancer-specific methylation pattern.

The teaching of Goessl et al. differ from the claimed method, at least in the fact that GSTP1 is a nucleic acid which bears a methylation pattern that is *specific for a type of cancer*, such as prostatic carcinomas. It is not used as a marker for the prostate organ. The difference

being that GSTP1 is a) also known to be methylated in other similar cancer types of different organs, for example breast and renal carcinomas, as reported by Esteller et al. in Cancer Research 58, 4515-4518 (Abstract), and b) the methylation pattern of GSTP1 detected by Goessl et al. was not even detectable in prostate tissue from individuals not suffering from prostate cancer. Hence without a medical history indicating a diseased prostate, detecting GSTP1 methylation (as described by Goessl) would only provide the information that the patient might suffer from a type of cancer, such as prostate cancer.

Therefore, it is incorrect to say that Goessl et al. teaches the detection of a methylation pattern to determine the presence of DNA from prostate tissue or organs, because this could only be provided by identifying a prostate (organ) specific methylation pattern on the GSTP1 gene, which is not methylated in the same way in other organs (diseased or not).

Detecting a methylation pattern in the circulating DNA which is characteristic for a specific organ or tissue, such as prostate however, is for the first time taught and disclosed in the current invention. This difference is essential and has neither been taught nor anticipated by Goessl et al., nor by Goessl as evidenced by Rein et al.

Applicants, therefore, respectfully request withdrawal of the Examiner's anticipation rejection, based on Applicants' claim amendments and rebuttal argument described herein.

## CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request entry of the present Amendment and allowance of the amended claim set provided herein. The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

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